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Remarks

Status of the Claims

Claims 1-9, 11-16, 18-21, 24-26 and 47 are pending in the present application. Applicants have amended claims 1 and 15 and added new claims 48 and 49. Support for claim 1 is found in the specification at least, for example, at page 5, lines 1-8. Support for claim 15 is found at least, for example, at page 5, lines 20-25. Support for claims 48 and 49 is found at least, for example, from page 18, line 14 to page 19, line 6, and in Example 7. Accordingly, upon entry of these amendments, claims 1-9, 11-16, 18-21, 24-26 and 47-49 will be pending and presented for consideration.

Claim Rejections Under 35 U.S.C. § 103

U.S. Patent No. 6,406,689 ("Falkenberg"); WO 93/20185 ("Steinman"); Sallusto *et al.*, (1994), Journal of Experimental Medicine, vol. 179, pp. 1109-1118 ("Sallusto"); de la Salle *et al.*, (1996), "FcγR on Human Dendritic Cells," Chapter 3, pp. 39-55 in Human IgG Fc Receptors, van de Winkel *et al.* (eds.), R.G. Landes Company ("de la Salle"); Hurn and Chantler, (1980), "Production of Reagent Antibodies," Chapter 5, vol. 70, pp. 104-142 in Methods in Enzymology, Academic Press, Inc. ("Hurn"); U.S. Patent No. 5,538,866 ("Israeli"); and U.S. Patent No. 6,429,199 ("Krieg")

Claims 1-3, 5-7, 14, 15, 18-20, 24 and 25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Falkenberg in view of Steinman, Sallusto, and de la Salle. Claims 1-3, 5-7, 14, 15, 18-20, 24 and 25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Hurn. Claims 1-3, 5-7, 14, 15, 18-20, 24 and 25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Israeli. Claims 1-3, 5-7, 14, 15, 18-21, 24 and 25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Krieg.

Claims 1-3, 5-7, 14, 15, 18-21, 24 and 25 relate to methods and compositions with a fusion protein comprising an antigen linked to an immunoglobulin (Ig) heavy chain constant region. Applicants submit that none of Falkenberg, Steinman, Sallusto, or de la Salle teaches or suggests any fusion protein, much less the fusion proteins recited in claims 1-3, 5-7, 14, 15, 18-21, 24 and 25. In addition, these references fail to teach or suggest a fusion protein that elicits a stronger immune response than an antigen alone.

Moreover, Falkenberg, Steinman, Sallusto, and de la Salle fail to provide any motivation for making or using a fusion protein comprising an immunoglobulin heavy chain constant region and lacking an immunoglobulin variable domain. Applicants submit that there can be no motivation to modify the immunoglobulins of Sallusto and de la Salle to omit immunoglobulin variable domains, as the immunoglobulins would lose their required specific binding affinity. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP § 2143.01. Since the modification of the immunoglobulins of Sallusto and de la Salle would render them unsatisfactory for their intended purpose (forming antigen-antibody complexes), Applicants submit that even in combination the cited references cannot render the claimed invention obvious.

Furthermore, Applicants submit that the claimed invention is not obvious because it benefits from unexpected advantageous properties not possessed or described by the cited art. "The discovery of new and unobvious properties in the claimed compounds rebuts even a *prima facie* case of obviousness where the art is silent on that property." *In re Albrecht*, 514 F.2d 1389, 1394 (C.C.P.A. 1975). Similarly, where a 35 U.S.C. § 103 rejection is based on structural similarities, "evidence of unobvious or unexpected advantageous properties may rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (citing *In re Papesch*, 315 F.2d 381, 386-87 (C.C.P.A. 1963)).

The fusion protein of the claimed invention possesses the new and unobvious property of eliciting a stronger immune response against an antigen in a mammal than the

antigen alone. Applicants have discovered that linking an Ig heavy chain constant region to an antigen causes a striking increase in the levels of antibodies generated by mice immunized with the fusion protein (see, *e.g.*, Application, Example 4; FIGS 5A and 5D; and page 12, lines 26-28). Specifically, mice immunized with Prostate-Specific Membrane Antigen (PSMA) generated essentially no primary immune response to the antigen (Application, page 38, lines 13-16 and FIG. 5A). In contrast, mice injected with Fc-PSMA consistently demonstrated a strong primary immune response to the antigen (Application, page 38, lines 18 and 19, and FIG. 5D). Applicants submit that the cited references do not describe a fusion protein that possesses this property, conferred by the fusion of an Ig heavy chain constant region to an antigen, and fails to appreciate that this modification of the antigen is able to generate greater amounts of antibody in immunized animals (*i.e.*, elicit a stronger immune response) than the antigen alone.

The art also failed to appreciate the advantages of using a fusion protein that benefits from this unexpected property. In particular, the modified antigen of the claimed invention is self-sufficient in eliciting a stronger immune response in a mammal. That is, efficient uptake and presentation of the modified antigen by antigen-presenting cells (APCs)-- a process required for eliciting an immune response-- does not require pre-binding of the antigen to another protein (*i.e.*, an antibody) that may prematurely dissociate from the antigen upon administration to a mammal. (Reversibility of an antibody-antigen interaction is well known. See, *e.g.*, Kurby, "Antigen-Antibody Interactions," Chapter 6, pp. 121-122, in Immunology, W.H. Freeman and Co., (1992), attached hereto as Exhibit A). Rather, the Ig heavy chain constant region of the claimed fusion protein is sufficient to selectively target the antigen to APCs for further processing (see, *e.g.*, Application, page 16, lines 12-22). Thus, the fusion protein of the present invention advantageously provides a consistent stoichiometry between the APC targeting portion and the linked antigen for eliciting a stronger immune response in a mammal than the antigen alone.

Thus, Applicants have discovered that the claimed methods and compositions have new and unobvious properties providing advantages in eliciting a stronger immune

response in a mammal than an antigen alone. Applicants submit that the art is silent about the newly discovered advantages of the claimed method and composition. Under *In re Albrecht*, the discovery of a new and unobvious property about which the art is silent rebuts even a *prima facie* case of obviousness. *In re Albrecht*, 514 F.2d at 1394. Applicants thus submit that the cited references cannot render obvious the claimed invention.

Like Falkenberg, Steinman, Sallusto, and de la Salle, Applicants submit that Hurn, Israeli, and Krieg fail to teach or suggest fusion proteins. These references also fail to provide any motivation for making or using a fusion protein comprising an antigen and an immunoglobulin heavy chain constant region. Accordingly, Applicants respectfully submit that these references do not cure the deficiencies of Falkenberg, Steinman, Sallusto, or de la Salle and thus fail to render obvious the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejections.

Falkenberg; Steinman; Sallusto; de la Salle; and U.S. Patent No. 6,277,375 ("Ward")

Claims 1-7, 11-16, 18-20, 24, 25 and 47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Ward.

The claimed invention relates to methods and compositions with a fusion protein comprising an antigen linked to an immunoglobulin heavy chain constant region whose ability to bind an Fc receptor is not modified by mutation; the fusion protein lacks an immunoglobulin domain. None of Falkenberg, Steinman, Sallusto, de la Salle, or Ward teaches or suggests a fusion protein with an immunoglobulin heavy chain constant region whose ability to bind an Fc receptor is not modified by mutation and lacks an immunoglobulin variable domain. In addition, these references fail to teach or suggest a fusion protein that elicits a stronger immune response than an antigen alone.

Furthermore, Falkenberg, Steinman, Sallusto, de la Salle, and Ward do not provide any motivation for modifying the teachings of these references. Applicants submit that there can be no motivation to modify the teachings of Ward to generate the claimed fusion proteins, since the proposed modification would render the immunoglobulin proteins of Ward unsatisfactory for their intended purpose. Ward describes mutant proteins with altered binding to Fc receptors, providing increased serum half-life (Ward, Abstract and col. 2, line 29, to col. 3, line 14). In contrast, the rejected claims require that Fc receptor binding is not modified by mutation. Therefore, modifying the immunoglobulin proteins of Ward to restore wild-type binding to Fc receptors would render them unsatisfactory for their intended purpose (providing increased serum-half life). Applicants thus submit that even in combination Falkenberg, Steinman, Sallusto, de la Salle, and Ward cannot render the claimed invention obvious.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-7, 11-16, 18-20, 24, 25 and 47 under 35 U.S.C. § 103(a).

Falkenberg; Steinman; Sallusto; de la Salle; U.S. Patent No. 5,709,859 ("Aruffo"); and Schlom, (1991), "Monoclonal Antibodies: They're More and Less Than You Think," Chapter 6, pp. 95-133 in Molecular Foundations of Oncology ("Schlom")

Claims 1-3, 5-9, 14, 15, 18-20, 24 and 25 stand rejected as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Aruffo and Schlom.

The rejected claims are drawn to methods and compositions with a fusion protein comprising an antigen and an immunoglobulin heavy chain constant region for eliciting an immune response against the antigen; the fusion proteins elicit a stronger immune response than an antigen alone. None of Falkenberg, Steinman, Sallusto, de la Salle, Aruffo, or Schlom teach or suggest eliciting an immune response with a fusion protein comprising an antigen linked to an immunoglobulin heavy chain constant region. In addition, these references fail to teach or suggest a fusion protein that elicits a stronger immune response than an antigen alone.

Furthermore, none of the references provides any motivation to generate fusion proteins that elicit an immune response. In particular, Falkenberg, Steinman, Sallusto, and de la Salle do not provide any motivation for generating fusion proteins. Additionally, Aruffo and Schlom, which do not relate to eliciting an immune response, fail to provide any motivation for generating fusion proteins comprising an antigen for eliciting a stronger immune response than the antigen alone. In fact, modifying a fusion protein of Aruffo to elicit an immune response against the fusion protein would destroy its intended use, *i.e.*, to block cell adhesion and/or cellular activation by binding to natural ligands on target cells (see Aruffo, col. 8, lines 41-44). Indeed, such an immune response would promote uptake and degradation of Aruffo's fusion proteins by APCs, thus destroying their ability to bind ligands on target cells. Therefore, Applicants submit that even in combination Falkenberg, Steinman, Sallusto, de la Salle, Aruffo, and Schlom cannot render obvious the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-9, 14, 15, 18-20, 24 and 25 under 35 U.S.C. § 103(a).

Falkenberg; Steinman; Sallusto; de la Salle; and U.S. Patent No. 6,086,875 ("Blumberg")

Claims 1-3, 5-7, 14, 15, 18-20, 24 and 25 stand rejected as allegedly unpatentable over Falkenberg, Steinman, Sallusto, and de la Salle in view of Blumberg.

The claimed invention relates to methods and compositions with a fusion protein for eliciting an immune response against an antigen, wherein the composition is administered to the mammal intramuscularly, intravenously, transdermally or subcutaneously. Applicants submit that that none of Falkenberg, Steinman, Sallusto, de la Salle, and Blumberg provides any motivation to generate the claimed methods and compositions.

Applicants submit that there can be no motivation to modify the teachings of Blumberg to generate the claimed invention, as the proposed modification would render Blumberg's invention unsatisfactory for its intended purpose. The purpose and benefit of Blumberg's invention is to deliver an immunogen across a mucosal surface (*i.e.*, an

epithelial barrier) via, for example, oral, intrapulmonary, intrabiliary and intranasal administration (see Blumberg, col. 4, lns. 44-60 and col. 9, lns. 58-65). Mucosal surfaces represent "the first portal of entry for many diseases" and are capable of triggering "the first line of defense against many pathogens, that is, mucosal immunity" (see Blumberg, col. 4, lns. 54-60 and col. 2, lns. 44-50). In contrast, the claimed invention relates to intramuscular, intravenous, transdermal or subcutaneous administration of proteins. Thus, modifying Blumberg's invention to avoid delivery across a mucosal surface would render it unsatisfactory for its intended purpose. Accordingly, Applicants submit that the combined references cannot render obvious the claimed invention and respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-7, 14, 15, 18-20, 24 and 25 under 35 U.S.C. § 103(a).

Conclusion

Claims 1-9, 11-16, 18-21, 24-26, 47-49 are pending and believed to be in condition for allowance. Dr. Canella is invited to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,

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CHAPTER

6

Antigen-Antibody Interactions

The antigen-antibody interaction is a bimolecular association similar to an enzyme-substrate interaction but with the important distinction that it does not lead to an irreversible chemical alteration in either the antibody or antigen and therefore is reversible. The interaction between an antibody and an antigen involves various noncovalent interactions between the antigenic determinant, or epitope, of the antigen and the variable-region (V_H/V_L) domain of the antibody molecule, particularly the hypervariable regions, or complementarity-determining regions (CDRs). The exquisite specificity

of an antibody for an antigen has led to the development of a variety of immunologic assays. These assays can be used to detect the presence of either antibody or antigen and have played vital roles in diagnosing diseases, monitoring the level of the humoral immune response, and identifying molecules of biological or medical interest. These assays differ in their speed and their sensitivity; some are strictly qualitative, and others are quantitative. In this chapter, the nature of the antibody-antigen interaction is examined, and various immunologic assays that measure this interaction are described.

Strength of Antigen-Antibody Interactions

The noncovalent interactions that form the basis of antigen-antibody binding include hydrogen bonds, ionic bonds, hydrophobic interactions, and van der Waals interactions (Figure 6-1). Because the strength of each of these interactions is weak (compared with that of a covalent bond), a strong antigen-antibody interaction requires a large number of such interactions. Furthermore, each of these noncovalent interactions operates over a very small distance, generally less than 1×10^{-7} mm (1 angstrom, Å); consequently, a strong antigen-antibody interaction depends on a very close fit between the antigen and antibody, which is reflected in the high degree of specificity characteristic of antigen-antibody interactions.

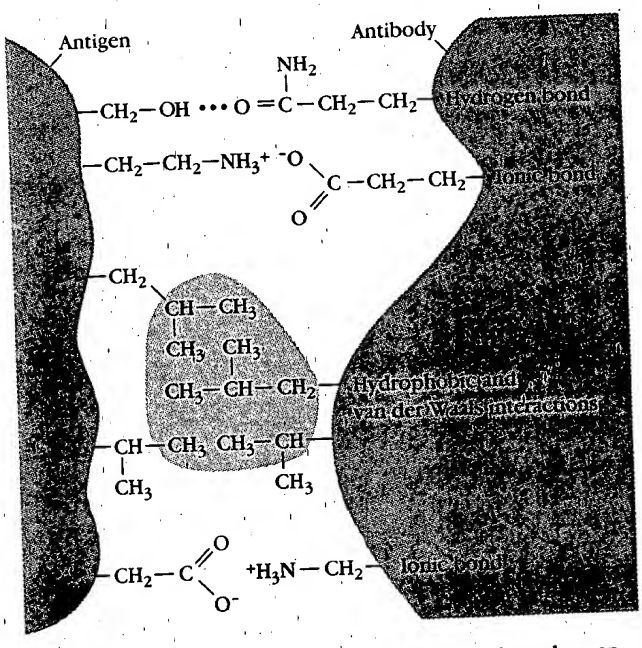

Figure 6-1 The interaction between an antibody and an antigen depends on four types of noncovalent forces: (1) ionic bonds between oppositely charged residues, (2) hydrogen bonds in which a hydrogen atom is shared between two electronegative atoms, (3) hydrophobic interactions in which water forces hydrophobic groups together to maximize hydrogen bonding of water molecules, and (4) van der Waals interactions between the outer electron clouds of two atoms. In an aqueous environment noncovalent interactions are extremely weak and depend upon close structural complementarity between antibody and antigen.

Antibody Affinity

The strength of the sum total of noncovalent interactions between a single antigen-binding site on an antibody and a single epitope is the *affinity* of the antibody for that epitope. Low-affinity antibodies bind antigen weakly and tend to dissociate readily, whereas high-affinity antibodies bind antigen more tightly and remain bound longer. The association between a binding site on an antibody (Ab) with a monovalent antigen (Ag) can be described by the equation

$$\text{Ag} + \text{Ab} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Ab} - \text{Ag}$$

where k_1 is the forward, or association, rate constant and k_{-1} is the reverse, or dissociation, rate constant. The ratio of k_1/k_{-1} is the association constant K, a measure of affinity. It can be calculated from the ratio of the concentration of bound antigen-antibody to the concentrations of unbound antigen and antibody, as follows:

$$K = \frac{k_1}{k_{-1}} = \frac{[\text{Ab} - \text{Ag}]}{[\text{Ab}][\text{Ag}]}$$

K values vary for different antibody-antigen complexes and depend upon both k_1, which is expressed in liters/mole/second (L/mol/s) and k_{-1}, which is expressed in 1/second. For small haptens, the forward rate constant can be extremely high; in some cases k_1 values can be as high as 4×10^8 L/mol/s, approaching the theoretical upper limit of diffusion-limited reactions (10^9 L/mol/s). For larger protein antigens, however, k_1 is smaller, with values in the range of 10^5 L/mol/s. The rate at which bound antigen leaves an antibody's binding site (or the dissociation rate constant, k_{-1}) plays a major role in determining the antibody's affinity for an antigen. Table 6-1 illustrates the role of k_{-1} in determining the association constant K for several antibody-antigen interactions. For example, the k_1 for the DNP-L-lysine system is about one-fourth that for the fluorescein system, but its k_{-1} is 200 times greater; consequently, the K for the fluorescein system is about a thousandfold higher than K for the DNP-L-lysine system. Low-affinity antibody-antigen complexes have K values between 10^4 and 10^5 L/mol; high-affinity complexes can have K values as high as 10^{11} L/mol.